Selection of Control, Randomization, Blinding, and Allocation Concealment

Abstract

Clinical trials looking at which treatment is better must have certain checks in place. Appropriate "control" selection while comparing the investigating agent to the "control group is essential to rule out selection bias. Randomization is another step to minimize variability or "confounders." By randomization, research participants have an equal chance of being selected into any treatment group of the study, generating comparable intervention groups, thereby distributing the confounders. A trial can be "open labeled" or "blinded." By the process of blinding, we make the participant and/or assessing physician unaware of the treatment he/she is going to receive. Thus, the element of bias which can creep in owing to personal preference or subjective component to the assessment of outcome can be eliminated. Concealment of allocation is done as the participant enters the trial. Concealment secures randomization and prevents "selection bias".

Keywords: *Allocation concealment, blinding, clinical trial, control, randomization, SNOSE*

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Introduction

Clinical trials or interventional studies are to be designed in such a way that it gives a comprehensive idea about the effectiveness/efficacy or safety of any new agent introduced for the treatment of any clinical condition. To understand the fact that the improvement (or deterioration) is not happening *by chance,* it is essential that the treatment modality is compared against another modality of treatment (active control) or no treatment (placebo control). Thus, the role of having control is paramount, and it decides the level of evidence of any trial and in-turn decides the grade of recommendation.

Apart from having control, there is another important factor which can affect the interpretation of result in any clinical trial, and this factor is "bias." The bias can be while selecting the participant and the control (selection bias), owing to the confounding factors (confounding bias) and also while assessing the outcome (assessment bias). Randomization is the method adopted to eliminate the bias of selection and confounder. It has got two steps; generation of random number and concealment of the random number from the dispensing physician (allocation concealment). For eliminating the assessment bias, the method adopted is blinding and it can be done at a different level using the participant of the trial, assessing physician, and even the statistician analyzing the results.

The article will attempt in elaborating on these facets of clinical trial and impart practical clues to implement the same.

A. Selection of control- The "control" is used in clinical trials to nullify the effect of known or unknown factors (other than the factor being tested) on the research outcome and hence, to increase the reliability of the results. For example, if a new topical medication is shown to be effective in psoriasis patient, the inclusion of "control" in the study allows the investigator to conclude that the new medication is truly effective and improvement did not happen by chance.

Controls in case-control studies:

While choosing control, two principles should be followed:[1]

i. The control or the comparison group should be representative of the source population from which cases are derived
ii. The controls should be independent of the exposure, i.e., less likely to have the exposure of interest.

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For e.g., to test the role of "topical corticosteroids causing the unresponsiveness to standard antifungal therapy" it is essential that case (those who have used steroid) and control (those who have not) be chosen from the same socio-cultural strata to eliminate the confounders such as hot and humid working environment, cleanliness, etc. This prevents "selection bias." Thus, a control minimizes the effects of variables other than the variable under evaluation.

Controls in clinical trials:

In making a decision about a new treatment, the control arm is usually taken as the "gold standard treatment" (or the "best available treatment"). Comparison between the "test" arm (or "experimental" arm) and the "control" arm in such clinical studies makes a fruitful assessment of the new treatment compared with the previous one and increases the reliability of the study.

i. Placebo control: A placebo is an inactive substance that looks like the drug or treatment being tested.[2] A placebo control may be used where no standard treatment exists or else using a placebo control becomes unethical and substandard care in patients with active disease, where there is an approved treatment. Guidelines state that there should be a condition of "clinical equipoise" before a placebo-controlled trial is started. Clinical equipoise assumes that there exists not one better intervention either for the control or experimental group during the design of the trial, e.g., a trial on systemic sclerosis by using an experimental drug understanding the fact that there is no gold-standard therapy for systemic sclerosis.[3] The use of "active" control or "historical" control (stated below) can address this issue. Participants who are going to receive placebo are not going to benefit from the trial. This therapeutic misconception should be eliminated during the informed consent process.
ii. Dose-response control: A new dose for a known drug makes it a "new drug."[4] During its clinical trial, the control is usually the previously used dose. For e.g., 10 mg levocetirizine compared to 5 mg levocetirizine
iii. Active control: Here, the control is an active drug, usually the standard therapy or known effective treatment
iv. Historical control: Such control uses data from previously conducted studies and administrative databases. The studies that can be chosen for historical control can be a prospective natural history study or a control group from a previous randomized controlled trial.

B. Randomization

Minimizing variability of evaluation is the core of conducting good research or experiment. This variability is also known as "confounders." Confounders can be known or unknown. Confounders have the possibility of generating erroneous results because of the unknown effects of unmeasured variables. The process by which confounders can be reduced is known as "randomization." By randomization, research participants have an equal chance of being selected into any treatment group of the study, generating comparable intervention groups, thereby distributing the confounders. The confounders can, therefore, be ignored. Thus, the difference in outcome and results can be explained by treatment alone. However, if one wants to gain greater experience using a new treatment or drug, one may opt for "Unequal randomization"- randomization in 2:1 ratio (2/3 of patients on new treatment). The power of the study does get reduced [power decreases from 0.95 (for 1:1) to 0.925 (for 2:1)], but this technique is statistically feasible and is especially suited to phase II randomized trials.

Benefits of randomization:

i. Balances the treatment groups with respect to baseline variability, known, and unknown confounding factors, thus eliminates "confounding bias"
ii. Eliminates "selection bias." Selection bias occurs when the researcher voluntarily or involuntarily steers the less sick patients to the treatment he feels is better and vice versa
iii. Forms the basis for statistical tests.

How to randomize?

i. Computer generated random number table. The statistical software has a provision of choosing equal or unequal randomized groups, choosing stratification, etc
ii. Random number table from statistical textbooks
iii. For smaller experiments: tossing coins (heads-control and tails-treatment), roll of dice (≤3-treatment and >3-control), and shuffled deck of cards (even-Group A and odd-Group B). However, these methods are replaced by the aforementioned methods.

What is not randomization?

i. Alternate assignment: Study participants alternatively assigned to treatment, e.g., Odd numbers go to Treatment A and even numbers go to Treatment B
ii. Assignment according to the date of entry to study, e.g., 2 weeks of the month to Group A, next 2 weeks to Group B
iii. Assignment according to the days of the week, e.g., Monday OPD patients to Group A, Wednesday OPD patients to Group B. This gives rise to Berksonian bias.

Techniques for randomization

i. Simple randomization: Randomization according to a single sequence of random assignments is known as simple randomization.[5] Assignment to

the treatment groups is random and not concerned with other variables. For e.g. toss of coin, roll of dice, etc. This is the most simple and easy approach of randomization. In clinical studies with large sample size (at least 1,000 participants), simple randomization usually balances the number of subjects in each group. However, simple randomization could be problematic in smaller samples resulting in an unequal number of participants in treatment arms

ii. Block randomization: Block randomization ensures that the number of participants in the study groups is nearly equal. Such equal groups may be required in large sample size studies and where a long follow-up period is expected. Under such circumstances inequality between groups is possible. Block randomization is done by creating blocks of sequences, which will ensure that the same number of participants will be allocated to the study groups within each block.[6] Blocks are small and balanced. The block size is determined by the researcher (with two treatment arms, block size of 4, 6, and 8).[7] The blocks are used in small increments as researchers can more easily control balance. The blocks may be fixed or permutable. However, block size should not be known to investigators otherwise the last treatment in each block is predictable. To reduce such bias, the block size can be varied over time, even randomly

e.g., Block randomization of two treatment groups A and B, number of blocks = 5, size of blocks = 10, and fixed size blocks.

BLOCK 1
1: A 2: B 3: B 4: A 5: A 6: B 7: B 8: A 9: B 10: A
BLOCK 2
1: A 2: B 3: B 4: B 5: A 6: B 7: A 8: A 9: B 10: A
BLOCK 3
1: A 2: B 3: B 4: A 5: B 6: A 7: B 8: A 9: A 10: B
BLOCK 4
1: A 2: B 3: B 4: B 5: B 6: A 7: A 8: A 9: A 10: B
BLOCK 5
1: B 2: A 3: B 4: A 5: B 6: A 7: B 8: B 9: A 10: A

iii. Stratified randomization: When specific variables are known to influence the outcome, stratification of the sample is required to keep the variables (e.g., age, gender, weight, prognostic status, etc) as similar as possible in between the treatment groups. This method achieves a balance between baseline characteristics. At first, variable is identified, strata is created. Participants are assigned to strata. Simple randomization is then applied to each stratum to assign subjects to either group, e.g. in case of assessing results of immunotherapy for viral warts, stratification can be done with respect to the types of warts viz. verruca vulgaris, verruca plana, plantar wart, condyloma acuminata.

iv. Cluster randomization: This method randomizes groups of people instead of individuals. This method is also known as "group randomization." Cluster randomization is particularly favored to avoid complaint among the group of people living in close vicinity, e.g., vaccine trials where all participants of the same locality receive the same vaccine, lifestyle modification studies, and studies involving nutritional interventions. Here, sampling units are groups and not individuals.

C. Blinding

A trial can be "open labeled" or "blinded". By the process of blinding, we make the participant and/or assessing physician unaware of the treatment he/she is going to receive. Thus, the element of bias which can creep in owing to personal preference or subjective component to the assessment of outcome (e.g., a tool like physician global score is used to assess the outcome) can be eliminated. The process has now been further extended to include the statistician analyzing the result to make it fool proof. Thus, blinding is helpful in eliminating intentional or unintentional bias, increasing the objectivity of results, and ensuring the credibility of study conclusions.

Types of blinding:

i. Open-labeled or unblinded: All parties involved in a study are aware of the treatment the participants are receiving. Although blinding is desirable, sometimes it may not be possible or feasible. This type of study design suffers from low credibility but may be acceptable if endpoints are indisputably objective (e.g., survival or death)

ii. Single-blind: The participants in a study might drop out from study or might give false assessment if they come to know that they are receiving "no treatment." In addition, they might develop a placebo effect, if they know they are receiving "new treatment." All these biases can be eliminated by single-blinding. In this, a group of individuals (usually the participants) do not know the intervention he or she is going to receive. Conventionally, it refers to participant-blinded but logically the group of individuals blinded can also be the outcome assessor. Thus, a single-blind trial can be either participant-blind or assessor-blind, and it is better to specify who is blinded, instead of saying single-blind

iii. Double-blind: Like participants, the investigator/observer may influence the results of the study, if they are aware if a group of individuals are receiving a particular treatment. For example, if the endpoint is subjective (e.g. physician global scale), they might record a more favorable response for treatment of their preference. In addition, they might influence participants' assessment of a particular treatment

during follow-up meetings. In double-blinding, neither the participant nor the investigator/observer/outcome assessor is aware of the treatment allotted. The investigator is the person carrying out the research. The observer or the outcome assessor is the person who assesses the parameters of the study

iv. Triple-blind: Triple-blinding is done to eliminate the bias of data analysts. In triple-blinding, the participant, investigator, and the data analyst are unaware of the treatment given.

However, instead of expressing whether the trial is single, double, or triple blinded, it is more pertinent to specify who exactly is going to be blinded.

Masking: It is a term used interchangeably with "blinding" and is usually used by ophthalmologists.

Advantages of blinding:

i. Avoids observation bias. For e.g., during the evaluation of a subjective score like urticaria severity score, blinding prevents favoring of the test drug by the investigator
ii. Can also reduce the opportunity for bias to enter into the evaluation of the trial results owing to the knowledge of the treatment.

Procedures of blinding a trial:

i. By using identical looking dosage forms, for e.g. in a placebo-controlled trial, the placebo used should be similar looking in shape, size, color, and odor as that of the active drug
ii. If the two active drugs to be used in a trial are dissimilar in shape, size, color one can opt for a **"double dummy, double blind trial."** Here, two placebo tablets are to be used, which are similar to the active drugs. Each person, thus, receives two drugs, one active and one placebo as follows:

Investigational group = Active drug + Placebo

Control group = Placebo + Active control

iii. If the active drugs are dissimilar and double-dummy is not available, one can make use of some other methods, which are not as foolproof as the double-dummy method. These methods are prone to get unblinded at any point of trial conduction
    a. Both the active drugs can be taken out from their packaging and repacked in similar looking opaque containers. The containers can be labeled according to randomization
iv. The observer can be blinded by separating the room where the person is dispensing the drug and the person observing the effects of the drug.

Assessment of the efficacy of blinding:

There might be untoward effects in which the trial can be unblinded. The curiosity of participants or staff, differences in taste and smell of the drug, and placebo or a cross-over study are such instances. Ideal placebos are not always easy to procure or manufacture. Thus, the assessment of blinding should be done prior to the decoding of randomization. The participants, investigators, and staff are asked to guess what the participants had received. If the guess is 50% in each group, blinding has been maintained. If the guess is >50%, there had been a breach in blinding. If guess is <50% a suspicion about non-admittance of breach of blinding should be made.

Instances when blinding may be broken:

i. The study is completed and data analyzed
ii. For individual patient during an emergency, e.g., road traffic accident due to an antihistamine trial in urticaria, participant in psoriasis trial progressing to erythroderma.

Instances when blinding is not possible or difficult to achieve:

i. A surgical discipline is tested against a medical therapy, e.g., electrosurgery in pyogenic granuloma is tested against topical timolol
ii. "Sham procedure" is the improvisation, while working with surgical therapy that can be utilized to make it blinded, e.g., creating a dermal pocket without introducing any warty tissue against a regular auto-inoculation of wart can be done to make the placebo-arm blinded.[8] Ethical issues limits it uses of sham procedure, but in this instance, the authors have argued to have used the procedure to rule out the role of psychological effect, which has proven its role in wart therapy.

What to do if blinding is not possible or ethical:

I. Researchers should ensure that the outcomes being measured are as objective as possible
II. In addition, a duplicate assessment of outcome may be considered and researchers should report the level of agreement achieved
III. Expertise-based trial design- It can be done for surgical procedures, where patients are randomly assigned to different surgeons
IV. Partial blinding- Sometimes, independent blinded evaluators may be sufficient to reduce bias
V. Limitations and potential biases due to lack of blinding need to be acknowledged and discussed.

D. Allocation concealment

Concealment of allocation is done as the participant enters the trial. Concealment secures randomization and prevents "selection bias."

Every researcher tries to prove his hypothesis as correct. This can lead to conscious or unconscious steering of certain "good" patients to the desired group and others to the alternate group. If the investigator knows the randomization, such bias can lead to an imbalance in the study and wrong conclusions can be drawn. Such bias can be avoided by the following allocation of concealment techniques:

i. Third party randomization by phone or pharmacy. In large multi-centric trials, interactive-voice-response-service is used to ensure the allocation concealment in different centers
ii. Sequentially numbered, opaque, sealed envelope (SNOSE) technique: the randomization group is written on a paper and is kept in an opaque sealed envelope. The envelope is labeled with a serial number. The investigator opens the sealed envelope once the patient has consented to participate and then assigns the treatment group accordingly
iii. Sequentially numbered opaque containers: Similar to SNOSE, but here, instead of a piece of paper, the medicines are stored in opaque containers according to randomization, and there is no possibility of the dispenser to know which medicine is kept in which container.[9] Thus, the allocation is concealed.

E. Differences between allocation concealment and blinding

	Allocation concealment	Blinding
Purpose	Conceals randomization sequence	Makes participant or investigator or both unaware of the treatment received
Bias prevented	Selection bias	Observation bias
Time in the trial	Done when the patient enters the trial (during recruitment)	Occurs after the patient has entered the trial (after recruitment)

Conclusion

To conclude, a randomized controlled trial (RCT) is the gold-standard study design to evaluate any therapeutic method and carries the highest level of evidence (Level I b). Undoubtedly, as a researcher, we all are interested in conducting an RCT and contribute to the knowledge of the scientific world. Choosing the correct control group and avoiding biases are the most important aspect of any RCT. There can be a situation where blinding is not possible because of operational issues, but in every trial, effort should be thrust on randomization, which can eliminate two major biases: the bias of selection and confounding bias. Proper randomization would ensure that the baseline confounders are balanced lest; complex statistical methods are called for balancing them (e.g., multivariate analysis). This article is an attempt to provide practical tips for the researchers interested in a clinical trial, so that the data generated is more valid and credible.

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Conflicts of interest

There are no conflicts of interest.

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